1,026,502

PATENT SPECIFICATION

DRAWINGS ATTACHED

1,026,502

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Int. Cl.:—C 07 c // A 61 k

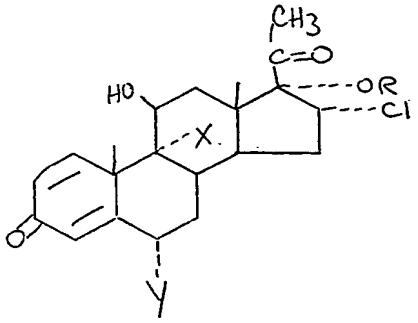
COMPLETE SPECIFICATION

Improvements in or relating to Steroids and the manufacture thereof

We, THE UPJOHN COMPANY, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to novel 16alpha-chloro steroids and processes for the preparation thereof as well as novel therapeutic compositions containing the new steroids.

The novel 16alpha - chloro steroid compounds of this invention are represented by the general formula: —



(I)

wherein X is hydrogen or fluorine, Y is hydrogen, methyl or fluorine, and R is hydrogen or the acyl radical of an organic carboxylic acid particularly a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms inclusive.

The compounds of Formula I and compositions thereof possess useful therapeutic properties, namely anti-inflammatory and glucocorticoid activity.

The compounds of Formula I and the compositions thereof are also useful in the treatment of inflammatory conditions of mammals and birds and are particularly useful in the treatment of inflammatory conditions of the skin, eyes and ears of humans and of valuable domestic animals, as well as contact dermatitis and other allergic reactions.

Administration of the novel steroids of formula I and compositions thereof can be in conventional dosage forms such as pills, tablets, capsules, syrups or elixirs for oral use, or in liquid forms which are adaptable to synthetic cortical steroid hormones for injectable products. The novel compounds of formula I can also be administered topically in the form of ointments, creams or lotions with or without coacting antibiotics, germicides or other materials forming advantageous combinations therewith.

The invention provides a method for the treatment of conditions such as rheumatoid arthritis, rheumatic fever, various dermatoses, eye and ear inflammations, joint (intra-articular) inflammation and adrenal hyperplasia. The compositions are advantageous for treating said conditions for reason of the improved ratio of therapeutic activity to undesirable side-effects, e.g. gastro - intestinal disturbances, salt retention or edema, known to exist with similar known therapeutically active steroids.

The novel compounds of this invention such as, 11beta,17alpha - dihydroxy - 16alpha-chloro - 1,4 - pregnadiene - 3,20 - dione,9 alpha - fluoro - 11beta,17alpha - dihydroxy-16alpha - chloro - 1,4 - pregnadiene - 3,20-dione,6alpha - fluoro - 11beta,17 alpha - dihydroxy - 16alpha - chloro - 1,4 - pregnadiene-3,20 - dione, 6alpha,9alpha - difluoro - 11beta, 17alpha - dihydroxy - 16alpha - chloro - 1,4-pregnadiene - 3,20 - dione,6alpha - methyl-11beta,17alpha - dihydroxy - 16alpha-chloro-1,4 - pregnadiene - 3,20 - dione, 6alpha -

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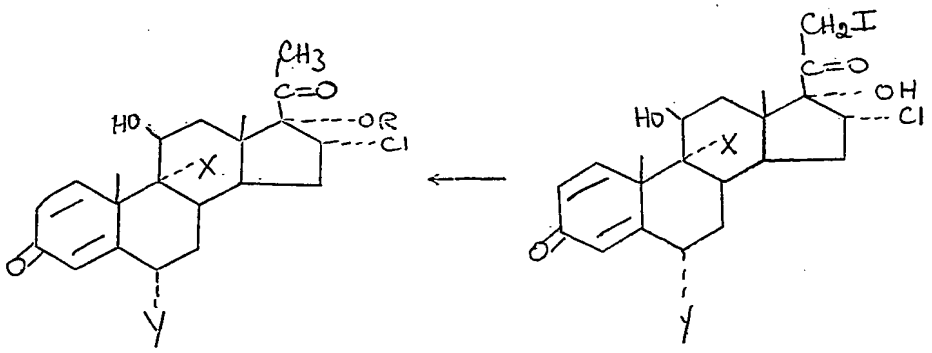
methyl - 9alpha - fluoro - 16alpha - chloro-11beta,17 - alpha - dihydroxy - 1,4 - pregnadiene - 3,20 - dione and the 17 - acylates thereof are prepared according to the following reaction scheme.



III II

wherein R, X and Y are as above defined.

The novel 21 - desoxy compounds of the present invention are obtained by treating for example the corresponding 11beta,17alpha-dihydroxy - 16alpha - chloro - 21 - iodo - 1,4 - pregnadiene - 3,20 - dione (II) with a reducing agent such as alkali metal thiosulphates, sodium sulphite,sodium bisulphite, other alkali metal sulphites or zinc and acetic acid to give the corresponding 11beta,17alpha-dihydroxy - 16alpha - chloro - 1,4 - pregnadiene - 3,20 - dione (III).

The preparation of compounds having the general formula II is described and claimed in our copending application 38760/62, Serial No. 1,026,501.

In carrying out the process of the present invention the starting material for example an 11beta, - 17alpha - dihydroxy - 16alpha - chloro - 21 - iodo - 1,4 - pregnadiene - 3,20-dione is reacted with a reducing agent such as sodium or potassium thiosulphate or sodium bisulphite. In the preferred embodiment of the invention a compound having the general formula II is slurried in acetic acid and thereto is added the aqueous solution of sodium or potassium thiosulphite or bisulphite. The mixture is then stirred at room temperature for a period of 10 minutes to 2 hours and the product is isolated from the reaction mixture by conventional methods such as filtration or extraction with a water immiscible organic solvent such as ether, benzene, methylene chloride, ethylene chloride, chloroform, hexane or heptane and evaporation of the extracts. Purification of the thus obtained 11beta,17alpha-dihydroxy - 16alpha - chloro - 1,4 - pregnadiene - 3,20 - dione is carried out by conventional means such as recrystallisation or chromatography.

The thus obtained 11beta,17 - alpha-dihydroxy - 16alpha - chloro - 1,4 - pregnadiene - 3,20 - dione can be selectively esterified for example with an acid anhydride in acetic acid solution and in the presence of an acid catalyst such as para - toluenesulphonic acid. The esterification is carried out usually at room temperature in a nitrogen atmosphere for several hours. The thus obtained ester namely the 11beta,17alpha - dihydroxy - 16 alpha - chloro - 1,4 - pregnadiene - 3,20-dione 17 - acylate is recovered from the reaction mixture by pouring the reaction mixture into water and separating the precipitated material or alternatively by extracting the product with water immiscible solvents such as benzene, ether, methylene chloride or ethylene chloride. The material thus obtained is purified through recrystallisation or chromatography to give pure esters.

The following non-limitative examples illustrate the process and products of the present invention.

Example 1

16α - chloro - 11β,17α - dihydroxy-1,4 - pregnadiene - 3,20 - dione

Two hundred milligrams of crude 6α-chloro - 11β,17α - dihydroxy - 21 - iodo-1,4 - pregnadiene - 3,20 - dione was slurried with 5 ml. of acetic acid and stirred for a period of 45 minutes. An aqueous solution of 250 mg. of sodium thiosulphate pentahydrate was added until the iodine colour disappeared. Additional water was added (50 ml.) and the mixture extracted with three 25 ml. portions of methylene chloride. The methylene chloride extracts were combined, washed with water and cold sodium bicarbonate solution until all acetic acid was neutralised. After drying over anhydrous sodium sulphate, the solution was concentrated to approximately 15 ml. and chromatographed by eluting with increasing proportions of acetone in Skellysolve B hex-

anes over 10 g. of Florisil—Registered Trade Mark (synthetic magnesium silicate). Fractions of 50 ml. were taken. The fractions containing the 16α - chloro - 11β,17α - dihydroxy - 1,4-pregnadiene - 3,20 - dione, as determined by papergram analyses, were combined and evaporated to give a residue which was recrystallised 3 times from methanol. The thus-obtained product was 16α - chloro - 11β,17α-dihydroxy - 1,4 - pregnadiene - 3,20 - dione.

In the same manner, by dehalogenating with sodium or potassium thiosulphate or other reducing agents such as zinc and acetic acid, sodium or potassium sulphites or bisulphites, other 21 - iodo compounds such as:

9α - fluoro - 16α - chloro - 11β,17α - dihydroxy - 21 - iodo - 1,4 - pregnadiene - 3,20-dione;

6α - fluoro - 16α - chloro - 11β,17α - dihydroxy - 21 - iodo - 1,4 - pregnadiene - 3,20-dione;

6α,9α difluoro - 16α - chloro - 11β,17α-dihydroxy - 21 - iodo - 1,4 - pregnadiene-3,20 - dione;

6α - methyl - 16α - chloro - 11β,17α - dihydroxy - 21 - iodo - 1,4 - pregnadiene-3,20 - dione;

6α - methyl - 9α - fluoro - 16α - chloro-11β,17α - dihydroxy - 21 - iodo - 1,4 - pregnadiene - 3,20 - dione

are converted into the corresponding 21-methyl steroids,

9α - fluoro - 16α - chloro - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione;

6α - fluoro - 16α - chloro - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione;

6α,9α - difluoro - 16α - chloro - 11β,17α-dihydroxy - 1,4 - pregnadiene - 3,20 - dione;

6α - methyl - 16α - chloro - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione;

6α - methyl - 9α - fluoro - 16α - chloro-11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione.

EXAMPLE 2

16α - chloro - 11β,17α - dihydroxy - 1,4-pregnadiene - 3,20 - dione 17 - acetate

A solution of 2.0 g. of 16α - chloro - 11β, 17α - dihydroxy - 1,4 - pregnadiene - 3,20-dione, 5 ml. of distilled acetic anhydride, 500 mg. of *p* - toluenesulphonic acid and 50 ml. of acetic acid was stirred at room temperature (about 25° C.) under a stream of nitrogen for 6 hours. The mixture was then poured with vigorous stirring into 500 ml. of water. The aqueous reaction mixture was extracted with two 250 ml. portions of chloroform, the extracts were combined, washed twice with water, then 200 ml. of 5% sodium hydroxide solution, again twice with water, dried over anhydrous sodium sulphate and evaporated to dryness. The dry residue was redissolved in acetone, poured onto a column of 75 g. alumina and chromatographed with 75 ml. of Skellysolve B hexanes containing increasing amounts of acetone. The fractions containing 16α - chloro - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione 17 - acetate as determined by papergram were combined, evaporated, and three times recrystallised from ethyl acetate to give crystalline 16α - chloro - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione 17-acetate.

Substituting other lower - hydrocarbon carboxylic acid anhydrides for the acetic anhydride is productive of other 16α - chloro - 11β,17α-dihydroxy - 1,4 - pregnadiene - 3,20 - dione 17 - acylates wherein the acyl radical of the acylate group is the acyl radical of, for example, a lower - aliphatic acid, e.g., formic (formic acid plus acetic anhydride), propionic, butyric, isobutyric, valeric, isovaleric, trimethylacetic, 2 - methylbutyric, 3 - ethylbutyric, hexanoic, diethylacetic, heptanoic, octanoic, α - ethyl - isovaleric, a cyclic acid, e.g., cyclopropylideneacetic, a cycloaliphatic acid, e.g., cyclopentylformic, cyclopentylacetic, β-cyclopentylpropionic, cyclohexylformic, cyclohexylacetic, β - cyclohexylpropionic, an aryl or alkaryl acid, e.g., benzoic, methylbenzoic, 3 - methyl - α - naphthoic, an aralkyl acid, e.g., phenylacetic, phenylpropionic, diphenylacetic or triphenylacetic.

In the same manner given in Example 2, other esters of substituted 16α - chloro - 11β, 17α - dihydroxy - 1,4 - pregnadiene - 3,20-diones can be made such as the acetate, propionate, hexanoate, benzoate, phenylacetate, laurate, and the like of 6α - fluoro - 16α-chloro - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione, 6α,9α - difluoro - 16α-chloro - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione, 6α - methyl - 16α - fluoro - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione, 6α - methyl - 9α - fluoro-16α - chloro - 11β,17α - dihydroxy - 1,4-pregnadiene - 3,20 - dione and 9α - fluoro-16α - chloro - 11β,17α - dihydroxy - 1,4-pregnadiene - 3,20 - dione.

The compositions of the present invention are preferably presented for administration in unit dosage forms such as tablets, capsules, powders, granules, sterile parenteral solutions or suspensions, oral solutions or suspensions, topical ointments, creams and lotions.

For oral administration either solid or fluid unit dosage forms can be prepared. For preparing solid compositions such as tablets, the principal active ingredient is mixed with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminium silicate, starch, lactose, acacia, and functionally similar materials as pharmaceutical diluents or carriers. The tablets can be laminated or otherwise compounded to provide a dosage form affording the advantage of prolonged or delayed action or predetermined successive action of the enclosed medication. For example, the tablet can comprise an inner

dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixture of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate. Alternatively, the two component system can be utilised for preparing tablets containing two or more incompatible active ingredients. Capsules, like tablets, are prepared by mixing the steroid with an inert pharmaceutical diluent and filling the mixture into a hard gelatin capsule of appropriate size. Soft gelatin capsules are prepared by machine encapsulation after preparing a slurry of the steroid with corn oil or other inert oil.

Fluid unit dosage forms for oral administration such as syrups, elixirs, and suspensions can be prepared. The water-soluble forms can be dissolved in an aqueous vehicle together with sugar, flavouring agents and preservatives to form a syrup. An elixir is prepared by using a hydro - alcoholic (ethanol) vehicle with suitable sweeteners such as sugar, saccharin, and cyclamate together with a flavouring agent. Suspensions can be prepared of the insoluble forms with a syrup vehicle with the aid of a suspending agent such as acacia, tragacanth or methylcellulose.

Typical ointments can be prepared by dispersing the steroid in a suitable ointment base such as petrolatum, lanolin, polyethylene glycols and mixtures thereof. Advantageously the steroid is finely divided by means of a colloid mill utilising light liquid petrolatum as a levigating agent. Creams and lotions are similarly prepared by dispersing the steroid in the oil phase of the system.

For parenteral administration, fluid unit dosage forms are prepared utilising the steroid and a sterile vehicle, water being preferred. The steroid, depending on the form and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the water - soluble steroid can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously adjuvants such as a local anesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into a vial and the water removed under vacuum: the dry lyophilised powder is then sealed in the vial and an accompanying vial of water for injection is supplied to reconstitute the powder prior to use. Parenteral suspensions are prepared in substantially the same manner except that the steroid is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The steroid can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the steroid.

The term unit dosage form as used in the specification and claims refers to physically discrete units suitable as unitary dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specifications for the novel unit dosage forms of this invention are indicated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for therapeutic use in humans and animals, as disclosed in detail in this specification, these being features of the present invention. Examples of suitable unit dosage forms in accord with this invention are tablets, capsules, pills, powder packets, granules, wafers, cachets, teaspoonfuls, tablespoonfuls, dropperfuls, ampoules, vials, segregated multiples of any of the foregoing, and other forms as herein described.

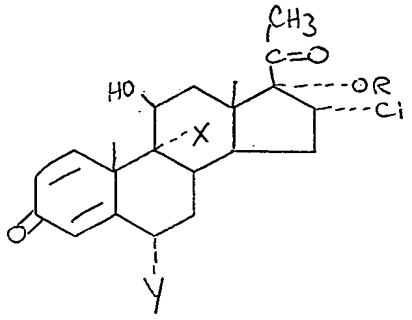
In addition to the administration of a compound of the formula I as the principal active ingredient of compositions for the treatment of the conditions described herein, the said compound of the novel compositions can be included with other types of compounds to obtain advantageous combinations of properties. Such combinations include a compound of the formula I with antibiotics such as chloramphenical, penicillin, tetracyclines, erythromycin, novobiocin, neomycin, polymyxin and bacitracin; analgesics such as aspirin, sodium salicylate, N - acetyl - *p* - aminophenol and salicylamide; agents which lessen pain by means of altering the subjects attitude such as the amphetamines and tranquilisers; local anesthetics such as benzocaine; procaine, and tetracaine; antacids such as calcium carbonate, aluminium hydroxide, basic aluminium carbonate, and bismuth subcarbonate; and the vitamins, especially ascorbic acid and the Vitaman B-complex.

The dosage of the compound of the formula I for treatment depends on route of administration, age, weight, and condition of the patient. A dosage schedule of from about 0.5 to about 10 milligrams, one to four times daily, embraces the effective range for the treatment of most conditions for which the compounds are effective. The compound of the formula I is compounded with suitable pharmaceutical carriers for convenient and effective administration. In the preferred embodiment of this invention the dosage units contain the steroid in

0.50, 1, 3 and 10 milligram amounts for systemic treatment and in 0.05, 0.1, 1 and 5% w/w concentrations for topical or localised treatment. The dosage of compositions containing the steroid and one or more other active ingredients is to be determined with reference to the usual dosage of each such ingredient.

WHAT WE CLAIM IS:—

1. A 16alpha - chloro steroid having the general formula:—



wherein X is hydrogen or fluorine, Y is hydrogen, methyl or fluorine, and R is hydrogen or an acyl radical of a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms inclusive.

2. 16Alpha - chloro - 11beta,17alpha - dihydroxy - 1,4 - pregnadiene - 3,20 - dione.

3. 6Alpha - methyl - 16alpha - chloro - 11beta,17alpha - dihydroxy - 1,4 - pregnadiene-3,20 - dione.

4. 6Alpha - fluoro - 16alpha - chloro - 11beta,17alpha - dihydroxy - 1,4 - pregnadiene-3,20 - dione.

5. 9Alpha - fluoro - 16alpha - chloro - 11beta,17alpha - dihydroxy - 1,4 - pregnadiene-3,20 - dione.

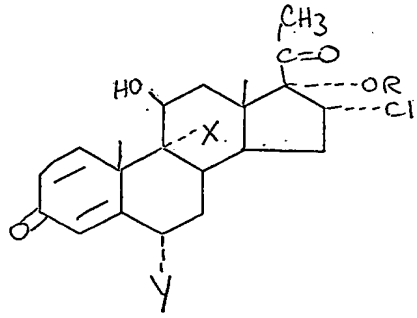
6. 6Alpha - methyl - 9alpha - fluoro - 16alpha - chloro - 11beta,17alpha - dihydroxy-1,4 - pregnadiene - 3,20 - dione.

7. 6Alpha,9alpha - difluoro - 16alpha - chloro - 11beta,17alpha - dihydroxy - 1,4-pregnadiene - 3,20 - dione.

8. 16Alpha - chloro - 11beta,17alpha - dihydroxy - 1,4 - pregnadiene - 3,20 - dione 17 - acylate, wherein the acyl group is of a hydrocarbon carboxylic acid containing from 1 to 12 carbon atoms inclusive.

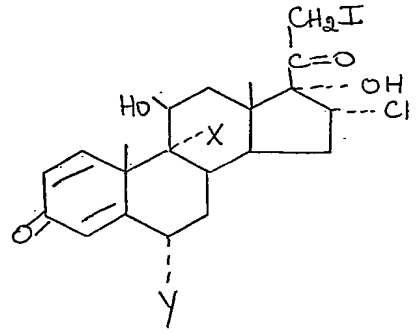
9. 16Alpha - chloro - 11beta,17 alpha - dihydroxy - 1,4 - pregnadiene - 3,20 - dione 17-acetate.

10. A process for the production of a compound of the formula (I)



I

wherein X is hydrogen or fluorine, Y is hydrogen, fluorine or methyl and R is hydrogen or the acyl radical of a hydrocarbon carboxylic acid, containing from 1 to 12 carbon atoms inclusive, which comprises reducing a 21-iodo steroid having the general formula (II),



II

wherein X and Y are as above defined with a halogen reducing agent, and then if desired esterifying in the 17-position.

11. A process as claimed in claim 10 wherein esterification is effected with an acid anhydride in acetic acid solution in the presence of an acid catalyst.

12. A process as claimed in claim 11 wherein the acid catalyst used is para - toluenesulphonic acid.

13. A process as claimed in claim 10, 11 or 12 wherein the reducing agent is an alkali metal thiosulphate, an alkali metal sulphite or zinc and acetic acid.

14. A process as claimed in claims 10, 11, 12 or 13 in which the starting material is 16α-chloro - 21 - iodo - 11β,17α - dihydroxy - 1,4-pregnadiene - 3,20 - dione or 9α - fluoro -

16α - chloro - 21 - iodo - 11β,17α - dihydroxy-1,4 - pregnadiene - 3,20 - dione.

15. A process as claimed in claims 10, 11, 12 or 13 in which the starting material is 6α-methyl - 16α - chloro - 21 - iodo - 11β,17α, dihydroxy - 1,4 - pregnadiene - 3,20 - dione or 6α - methyl - 9α - fluoro - 16α - chloro - 21 - iodo - 11β,17α,dihydroxy - 1,4 - pregnadiene - 3,20 - dione.

16. A process as claimed in claims 10, 11, 12 or 13 in which the starting material is 6α-fluoro - 16α - chloro - 21 - iodo - 11β,17α, dihydroxy - 1,4 - pregnadiene - 3,20 - dione or 6α,9α - difluoro - 16α - chloro - 21 - iodo-11β,17α,dihydroxy - 1,4 - pregnadiene - 3,20-dione.

17. A therapeutic composition comprising as the active ingredient a compound as claimed in any of claims 1 to 9 together with a pharmaceutically acceptable carrier.

18. A therapeutic composition as claimed in claim 17 in unit dosage form comprising from 0.5 to 10 mg. of the active ingredient.

19. A process for the preparation of a steroid as claimed in any of claims 1 to 9 substantially as herein described with reference to the Examples.

20. A steroid as claimed in any of claims 1 to 9 when prepared by a process as claimed in claims 10 to 16 or 19.

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